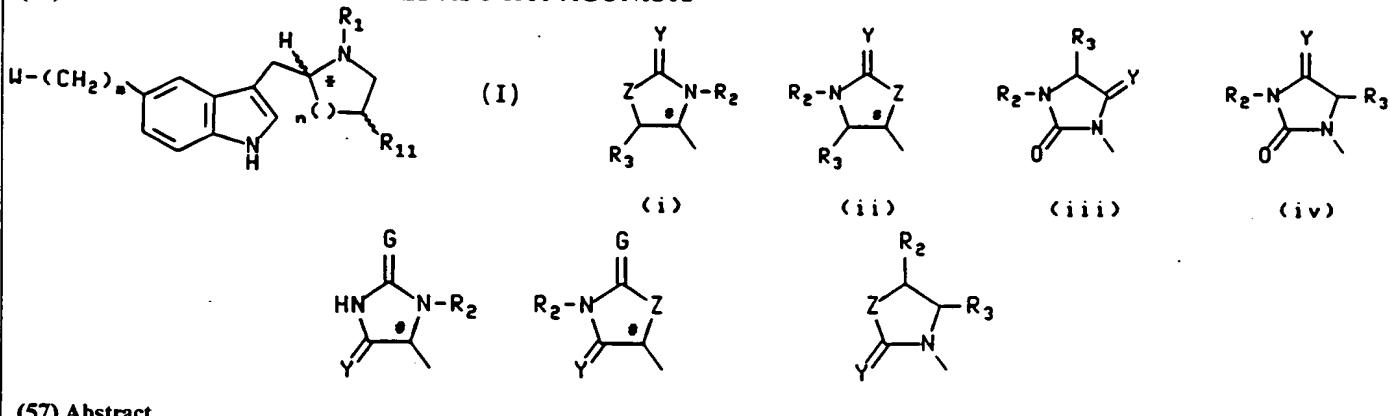




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(54) Title: INDOLE DERIVATIVES AS 5-HT1 AGONISTS



(57) Abstract

Compounds of formula (I) where W is (i), (ii), (iii), (iv), (v), (vi), or (vii); n is 0, 1 or 2; m is 0, 1, 2, or 3; Y and G are each independently oxygen or sulfur; Z is $-O-$, $-S-$, $-NH-$, or $-CH_2$; R₁ is hydrogen, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl substituted with one hydroxy, C₃ to C₈ alkenyl, C₃ to C₈ alkynyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or $-Q-R_4$; R₂ and R₃ are each independently hydrogen, C₁ to C₆ alkyl, aryl, C₁ to C₃ alkylaryl, or C₁ to C₃ alkylheteroaryl; R₄ is cyano, trifluoromethyl, $-COR_9$, $-CO_2R_9$, $-CONR_9R_{10}$, $-OR_9$, $-SO_2NR_9R_{10}$, or $-S(O)_qR_9$; R₉ and R₁₀ are each independently hydrogen, C₁ to C₈ alkyl, C₁ to C₃ alkylaryl, aryl, or R₉ and R₁₀ may together be taken to form a three-to seven-membered alkyl ring or a three-to seven-membered heteroalkyl ring having 1 heteroatom of O; Q is C₁ to C₃ alkyl; R₁₁ is hydrogen, $-OR_{12}$, or $-NHCOR_{12}$; R₁₂ is hydrogen, C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl; q is 0, 1, or 2; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy, and the pharmaceutically acceptable salts thereof. These compounds are useful in treating migraine and other disorders are new. These compounds are useful phsychotherapeutics and are potent serotonin (5-HT₁) agonists and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting antihypertensives and vasodilators.

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5 INDOLE DERIVATIVES AS 5-HT1 AGONISTS

Background of the Invention

The present invention relates to indole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in 10 treating migraine and other disorders.

United States Patents 4,839,377 and 4,855,314 and European Patent Application Publication Number 313397 refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent Application 040279 refers to 3-aminoalkyl-1H-indole-5-thioamides 15 and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Application Publication Number 303506 refers to 3-poly:hydro-pyridyl-5-substituted-1H-indoles. The compounds are said to have 5-HT₁ receptor agonist and vasoconstrictor activity and to be useful in treating migraine.

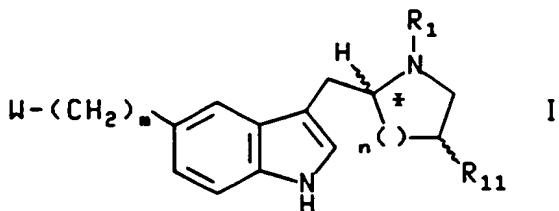
20 European Patent Application Publication Number 354777 refers to N-piperidinyl:indolyl:ethyl-alkane sulfonamide derivatives. The compounds are said to have 5-HT₁ receptor agonist and vasoconstrictor activity and to be useful in treating cephalic pain.

25 European Patent Applications Publication Numbers 438230, 494774, and 497512 refers to indole-substituted five-membered heteroaromatic compounds. The compounds are said to have 5-HT₁-like receptor agonist activity and to be useful in the treatment of migraine and other disorders for which a selective agonist of these receptors is indicated.

30 International Patent Application PCT/GB91/00908 and European Patent Application No. 313397A refers to 5-heterocyclic indole derivatives. The compounds are said to exhibit properties useful in the treatment and prophylaxis of migraine, cluster headache, and headache associated with vascular disorders. These compounds are also said to have "5-HT₁-like" receptor agonism.

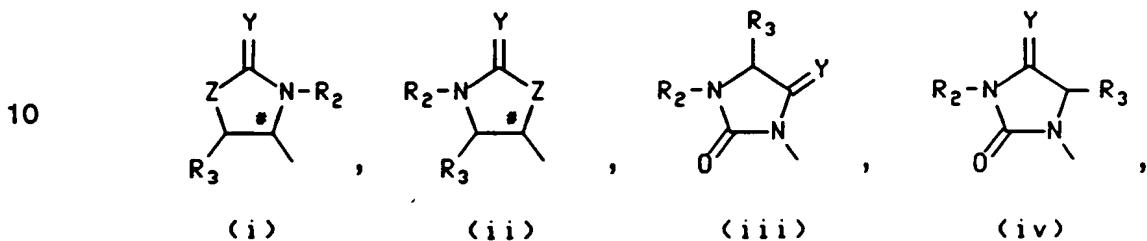
Summary of the Invention

35 The present invention relates to compounds of the formula

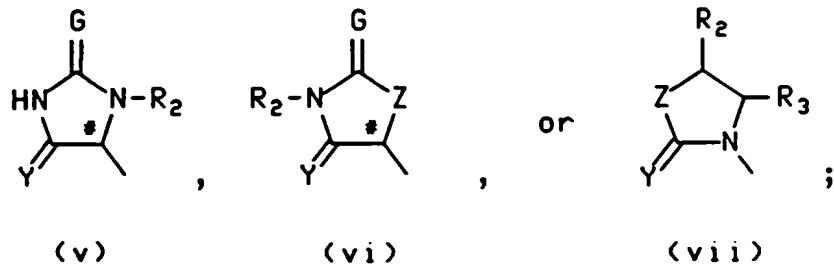


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where W is



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n is 0, 1, or 2; m is 0, 1, 2, or 3; Y and G are each independently oxygen or sulfur; Z is -O-, -S-, -NH, or -CH₂; R₁ is hydrogen, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl substituted with one hydroxy, C₃ to C₈ alkenyl, C₃ to C₈ alkynyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or -Q-R₄; R₂ and R₃ are each independently hydrogen, C₁ to C₈ alkyl, aryl, C₁ to C₃ alkylaryl, or C₁ to C₃ alkylheteroaryl; R₄ is cyano, trifluoromethyl, -COR₉, -CO₂R₉, -CONR₉R₁₀, -OR₉, -SO₂NR₉R₁₀, or -S(O)_qR₉; R₉ and R₁₀ are each independently hydrogen, C₁ to C₈ alkyl, C₁ to C₃ alkylaryl, aryl, or R₉ and R₁₀ may together be taken to form three-to seven-membered alkyl ring or a three- to seven-membered heteroalkyl ring having 1 heteroatom of O; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₈ alkyl, aryl, or C₁ to C₃ alkyl-aryl; q is 0, 1, or 2; Q is C₁ to C₃ alkyl; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl,

wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen (e.g., fluorine, chlorine, bromine or iodine), hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy, and the pharmaceutically acceptable salts thereof. These compounds are useful in treating migraine and other disorders.

5 The compounds of the invention include all optical isomers of formula I (e.g., R and S stereogenicity at any chiral site) and their racemic, diastereomeric, or epimeric mixtures. The epimers with the S absolute configuration at the chiral carbon site designated by # in formula I are preferred. When R₁₁ is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula I are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 0 or 1, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula I are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 2, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula I are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 0, the cis epimers [(2S, 3S) 10 absolute configuration in the azetidine ring] are particularly preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 1, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 2, the cis epimers [(2R, 5R) absolute configuration in the piperidine ring] are particularly 15 preferred.

20 Unless otherwise indicated, the alkyl, alkenyl, and alkynyl groups referred to herein, as well as the alkyl and alkylene moieties of other groups referred to herein (e.g. alkoxy), may be linear or branched, and they may also be cyclic (e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) or be linear or branched and contain cyclic moieties.

25 Preferred compounds of the invention are compounds of the formula I wherein W is (i), (ii), or (iii); n is 1; m is 1; R₁ is hydrogen, C₁ to C₃ alkyl, or -CH₂CH₂OCH₃; R₂ is hydrogen; and R₃ is hydrogen or -CH₂Ph (Ph=phenyl). Of the foregoing preferred compounds, the epimers with the S optical configuration at the chiral carbon designated by # in formula I are more preferred. Of the foregoing preferred 30 compounds, when R₁₁ is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula I are more preferred. Of the foregoing preferred compounds, when R₁₁ is -OR₁₂ or -NHCOR₁₂, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula

I are more preferred. Of the foregoing compounds, when R₁₁ is -OR₁₂ or -NHCOR₁₂, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred.

The following compounds are particularly preferred:

5 3-[(N-2-Methoxyethyl)pyrrolidin-2R-ylmethyl]-5-(2-oxo-1,3-oxazolidin-4S-ylmethyl)-1H-indole;

5-(2-Oxo-1,3-oxazolidin-4S-ylmethyl)-3-(pyrrolidin-2R-ylmethyl)-1H-indole; and

3-(N-Methylpyrrolidin-2R-ylmethyl)-5-(2-oxo-1,3-oxazolidin-4R,S-ylmethyl)-1H-indole.

10 The present invention also relates to a pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such 15 condition and a pharmaceutically acceptable carrier.

The present invention also relates to a method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal (e.g., a human) requiring 20 such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

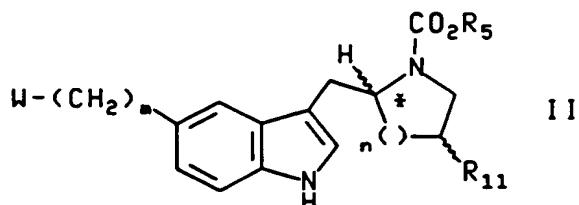
The present invention also relates to a pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising administering to a mammal (e.g., a human) requiring such treatment an 25 amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

The present invention also relates to a method for treating disorders arising from 30 deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising administering to a mammal (e.g., a human) requiring such treatment an amount of a compound of

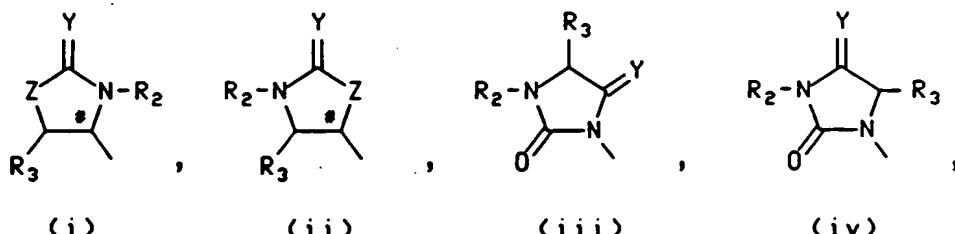
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the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

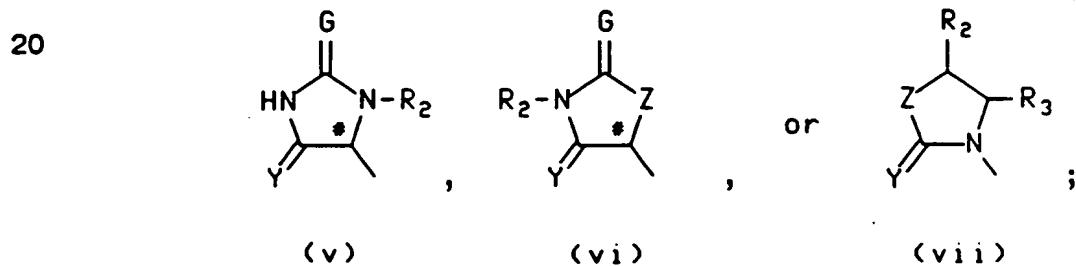
The present invention also relates to a compound of the formula



10 where W is



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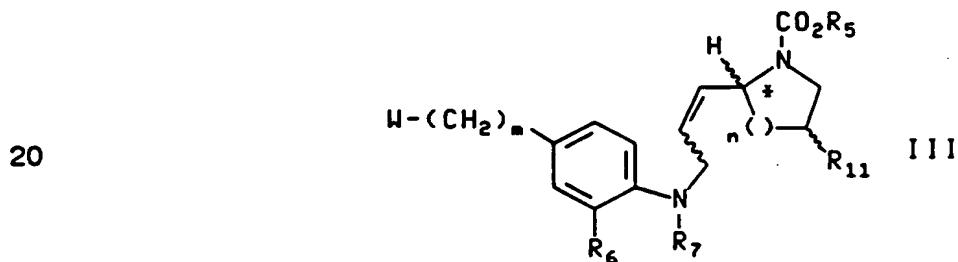


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n is 0, 1, or 2; m is 0, 1, 2, or 3; Y and G are each independently oxygen or sulfur; Z is -O-, -S-, -NH, or -CH₂; R₂ and R₃ are each independently hydrogen, C₁ to C₆ alkyl, aryl, C₁ to C₃ alkylaryl, and C₁ to C₃ alkylheteroaryl; R₅ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl (preferably benzyl); R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkyl-aryl; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to

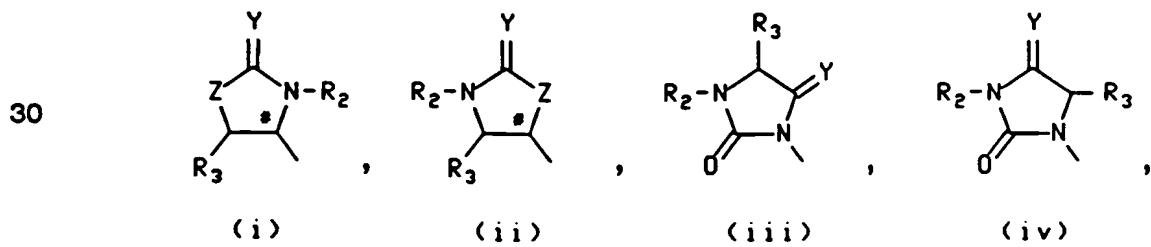
three groups selected from C₁ to C₄ alkyl, halogen (e.g. fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy. The epimers with the S absolute configuration at the chiral carbon site designated by # in formula II are preferred. When R₁₁ is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula II are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 0 or 1, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula II are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 2, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula II are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 0, the cis epimers [(2S, 3S) absolute configuration in the azetidine ring] are particularly preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 1, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 2, the cis epimers [(2R, 5R) absolute configuration in the piperidine ring] are particularly preferred. The compounds of formula II are useful as intermediates in preparing compounds of formula I.

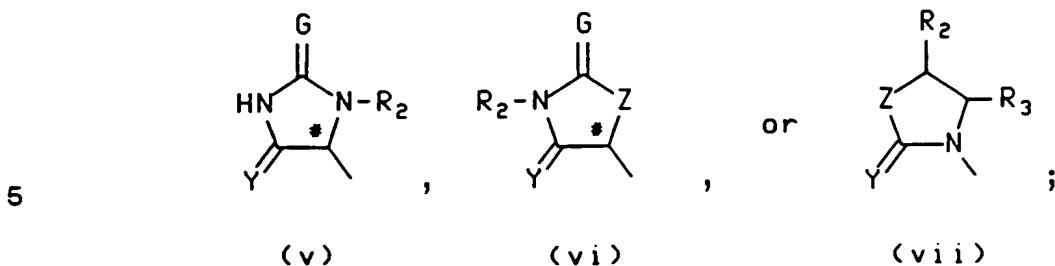
The present invention also relates to a compound of the formula



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where W is

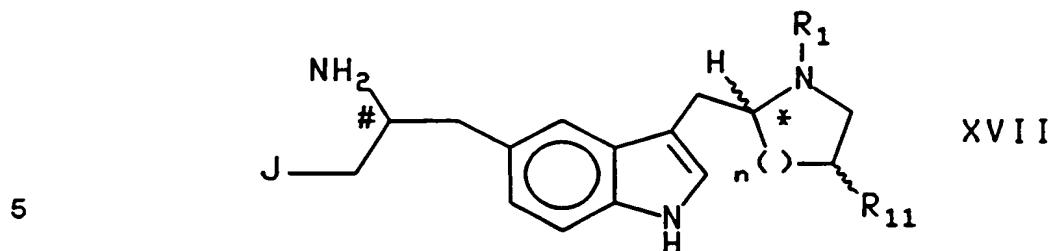




n is 0, 1, or 2; m is 0, 1, 2, or 3; Y and G are each independently oxygen or sulfur; Z is -O-, -S-, -NH, or -CH₂; R₂ and R₃ are each independently hydrogen, C₁ to C₆ alkyl, aryl, C₁ to C₃ alkylaryl, or C₁ to C₃ alkylheteroaryl; R₅ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl (preferably benzyl); R₆ is halogen [preferably bromide]; R₇ is -COCF₃, -SO₂CH₃, -SO₂Ph, or -CO₂C(CH₃)₃; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkyl-aryl; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy. The epimers with the S absolute configuration at the chiral carbon site designated by # in formula III are preferred. When R₁₁ is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula III are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 0 or 1, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula III are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 2, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula III are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 0, the cis epimers [(2S, 3S) absolute configuration in the azetidine ring] are particularly preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 1, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 2, the cis epimers [(2R, 5R) absolute configuration in the piperidine ring] are particularly preferred. The compounds of formula III are useful as intermediates in preparing compounds of formula II.

The present invention also relates to a compound of the formula

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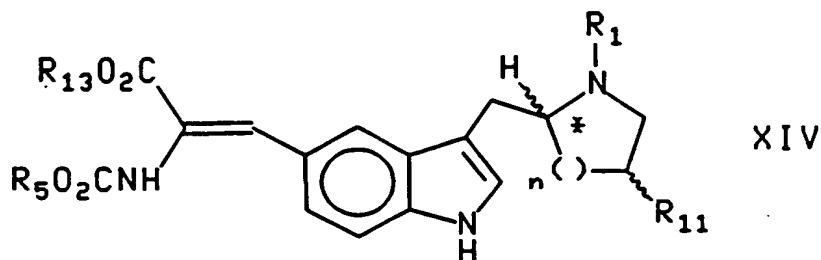
n is 0, 1, or 2; J is -OH or $-\text{CO}_2\text{R}_{13}$; R₁ is hydrogen, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl substituted with one hydroxy, C₃ to C₈ alkenyl, C₃ to C₈ alkynyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or -Q-R₄; R₄ is cyano, trifluoromethyl, $-\text{COR}_9$, $-\text{CO}_2\text{R}_9$, $-\text{CONR}_9\text{R}_{10}$, $-\text{OR}_9$, $-\text{SO}_2\text{NR}_9\text{R}_{10}$, or $-\text{S}(\text{O})_4\text{R}_9$; R₉ and R₁₀ are each independently hydrogen, C₁ to C₈ alkyl, C₁ to C₃ alkylaryl, aryl, or R₉ and R₁₀ may together be taken to form a three- to seven-membered alkyl ring or a three- to seven-membered heteroalkyl ring having 1 heteroatom of O; R₁₁ is hydrogen, $-\text{OR}_{12}$, or $-\text{NHCOR}_{12}$; R₁₂ is hydrogen, C₁ to C₈ alkyl, aryl, or C₁ to C₃ alkyl-aryl; R₁₃ is C₁ to C₈ alkyl, aryl, or C₁ to C₃ alkyl-aryl; q is 0, 1, or 2; Q is C₁ to C₃ alkyl; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy. The epimers with the S absolute configuration at the chiral carbon site designated by # in formula XVII are preferred. When R₁₁ is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula XVII are preferred. When R₁₁ is $-\text{OR}_{12}$ or $-\text{NHCOR}_{12}$ and n is 0 or 1, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula XVII are preferred. When R₁₁ is $-\text{OR}_{12}$ or $-\text{NHCOR}_{12}$ and n is 2, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula XVII are preferred. When R₁₁ is $-\text{OR}_{12}$ or $-\text{NHCOR}_{12}$ and n is 0, the cis epimers [(2S, 3S) absolute configuration in the azetidine ring] are particularly preferred. When R₁₁ is $-\text{OR}_{12}$ or $-\text{NHCOR}_{12}$ and n is 1, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred. When R₁₁ is

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-OR₁₂ or -NHCOR₁₂ and n is 2, the cis epimers [(2R, 5R) absolute configuration in the piperidine ring] are particularly preferred. The compounds of formula XVII are useful as intermediates in preparing compounds of formula I.

The present invention also relates to a compound of the formula

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n is 0, 1, or 2; R₁ is hydrogen, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl substituted with one hydroxy, C₃ to C₆ alkenyl, C₃ to C₆ alkynyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or -Q-R₄; R₅ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl; R₄ is cyano, trifluoromethyl, -COR₉, -CO₂R₉, -CONR₉R₁₀, -OR₉, -SO₂NR₉R₁₀, or -S(O)_qR₉; R₉ and R₁₀ are each independently hydrogen, C₁ to C₆ alkyl, C₁ to C₃ alkylaryl, aryl, or R₉ and R₁₀ may together be taken to form a three- to seven-membered alkyl ring or a three- to 20 seven-membered heteroalkyl ring having 1 heteroatom of O; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkyl-aryl; R₁₃ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkyl-aryl; q is 0, 1, or 2; Q is C₁ to C₃ alkyl; a first chiral carbon is designated by an asterisk; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, 25 wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy. The epimers with the S absolute configuration at the chiral carbon site designated by # in formula XIV are preferred. When R₁₁ is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula XIV are 30 preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 0 or 1, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula XIV are preferred. When R₁₁ is -OR₁₂ or -NHCOR₁₂ and n is 2, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula XIV

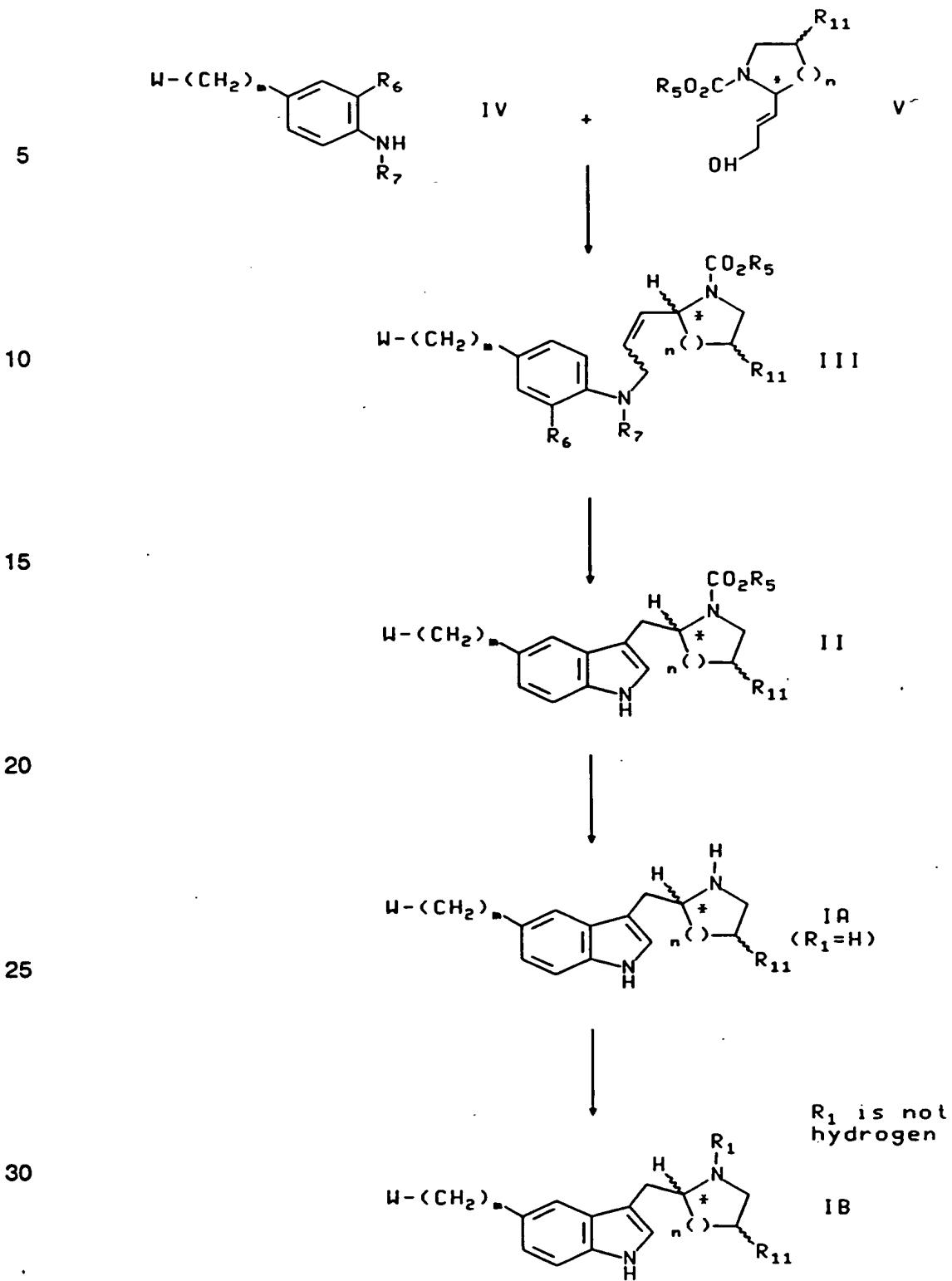
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are preferred. When R_{11} is $-OR_{12}$ or $-NHCOR_{12}$ and n is 0, the cis epimers [(2S, 3S) absolute configuration in the azetidine ring] are particularly preferred. When R_{11} is $-OR_{12}$ or $-NHCOR_{12}$ and n is 1, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred. When R_{11} is $-OR_{12}$ or $-NHCOR_{12}$ and n is 2, 5 the cis epimers [(2R, 5R) absolute configuration in the piperidine ring] are particularly preferred. The compounds of formula XIV are useful as intermediates in preparing compounds of formula XVII.

Detailed Description of the Invention

The compounds of the present invention are prepared via the following reaction 10 scheme.

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Compounds of formula III can be prepared by the Mitsunobu coupling reaction of compounds of formulas IV and V wherein W, n, m, R₅, R₆ (preferably bromide or iodide), and R₇ (preferably trifluoroacetyl [-COCF₃]) and R₁₁, are as defined above using a phosphine and an azodicarboxylate in an inert solvent. Suitable phosphines include 5 trialkyl phosphines and triarylphosphines, preferably triphenylphosphine. Suitable azodicarboxylates include dialkyl azodicarboxylates, preferably diethyl diazodicarboxylate. Suitable solvents include methylene chloride, ethers, (tetrahydrofuran, diethyl ether, and 1,4-dioxane), N,N-dimethylformamide and acetonitrile. The preferred solvent is tetrahydrofuran. The reaction is conducted at a 10 temperature of from about 0°C to about 65°C, most preferably at about 25°C.

Compounds of formula II can be prepared by the transition metal catalyzed cyclization of compounds of the formula III, wherein W, n, m, R₅, R₆ (preferably bromine or iodine), and R₇ (preferably trifluoroacetyl [-COCF₃]) and R₁₁, are as defined above, in a suitable inert solvent with a phase transfer catalyst and a base. Suitable transition 15 metal catalysts include palladium salts such as palladium (II) acetate or palladium (II) chloride and rhodium salts, such as tris(triphenyl)rhodium (I) chloride. The preferred catalyst is palladium (II) acetate. Suitable solvents include N,N-dimethylformamide, acetonitrile, and N-methylpyrrolidinone. The preferred solvent is N,N-dimethylformamide. Suitable phase transfer catalysts include tetraalkylammonium 20 halides, preferably tetra-n-butylammonium chloride. Suitable bases include tertiary amines, sodium hydrogen carbonate, and sodium carbonate. The preferred base is triethylamine. The reaction is conducted at a temperature of from about 60°C to about 180°C, preferably from about 80°C to about 100°C.

Compounds of formula IA wherein R₁ is hydrogen are prepared by catalytic 25 reduction of a compound of the formula II, wherein W, n, m, and R₅ are as defined above, R₅ is preferably benzyl, under an atmosphere of hydrogen, preferably at a pressure of from about 1 to about 3 atmospheres, or using a hydrogen source such as ammonium formate or formic acid in an inert solvent. Suitable catalysts include palladium on carbon, Raney nickel, and platinum oxide. The preferred catalyst is 30 palladium on carbon. Suitable solvents include C₁ to C₆ alcohols, N,N-dimethylformamide, ethyl acetate, and acetonitrile. The preferred solvent is ethanol. The reaction is conducted at a temperature of from about 0°C to about 60°C, preferably about 25°C.

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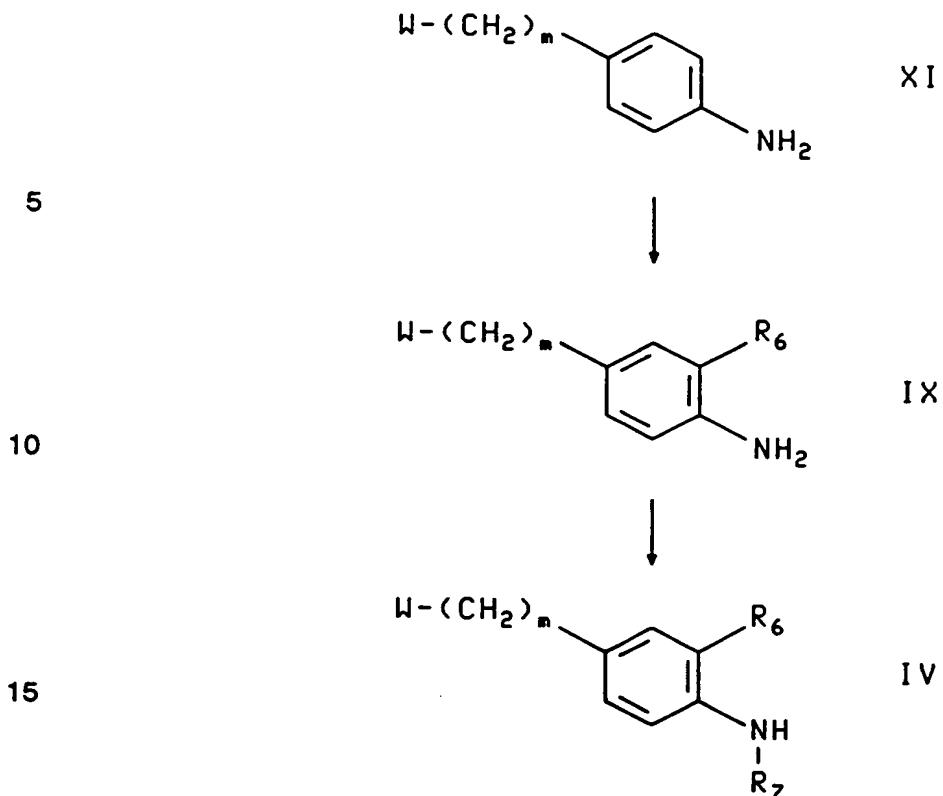
Compounds of formula IB wherein R₁ is not hydrogen can be prepared by the alkylation of a compound of formula IA wherein R₁ is hydrogen, and W, n, and m are as defined above with an alkylating agent of the formula R₁-LG and a base in an inert solvent, where LG is a suitable leaving group and R₁ is as defined above except for 5 hydrogen. Examples of suitable leaving groups include -I, -Br, -Cl, -OSO₂Ph, -OSO₂CH₃, and -OSO₂CF₃. Suitable alkylating agents include alkyl halides (chlorides, bromides, or iodides), alkyl tosylates, alkyl mesylates, alkyl triflates, α,β -unsaturated ketones, α,β -unsaturated esters, α,β -unsaturated aldehydes, α,β -unsaturated amides, α,β -unsaturated nitriles α,β -unsaturated sulfones, and α,β -unsaturated sulfonamides. 10 Alkyl halides (e.g. iodides) are preferred. Suitable bases include triethylamine, sodium carbonate, sodium hydrogen carbonate, and sodium hydroxide. The preferred base is triethylamine. Suitable solvents include methylene chloride, chloroform, carbon tetrachloride, acetonitrile, tetrahydrofuran, diethyl ether, dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, ethanol, propanol, methanol. The 15 preferred solvent is acetonitrile. The reaction is conducted between a temperature of from about 0°C to about 150°C preferably from about 25°C to about 65°C.

Compounds of formula IV can be prepared via the following reaction scheme:

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Compounds of formula IX can be prepared by reacting a compound of formula XI
20 wherein W and m are as defined above with either chlorine, bromine, or iodine in an
inert solvent with a base. Reaction with bromine is preferred. Suitable solvents include
C₁ to C₆ alcohols, methylene chloride, chloroform, or carbon tetrachloride. The
preferred solvent is methanol. Suitable bases include triethylamine, pyridine, sodium
carbonate, and sodium hydrogen carbonate. The preferred base is sodium hydrogen
25 carbonate. The reaction is conducted at a temperature of from about 0°C to about
65°C, preferably at about 25°C.

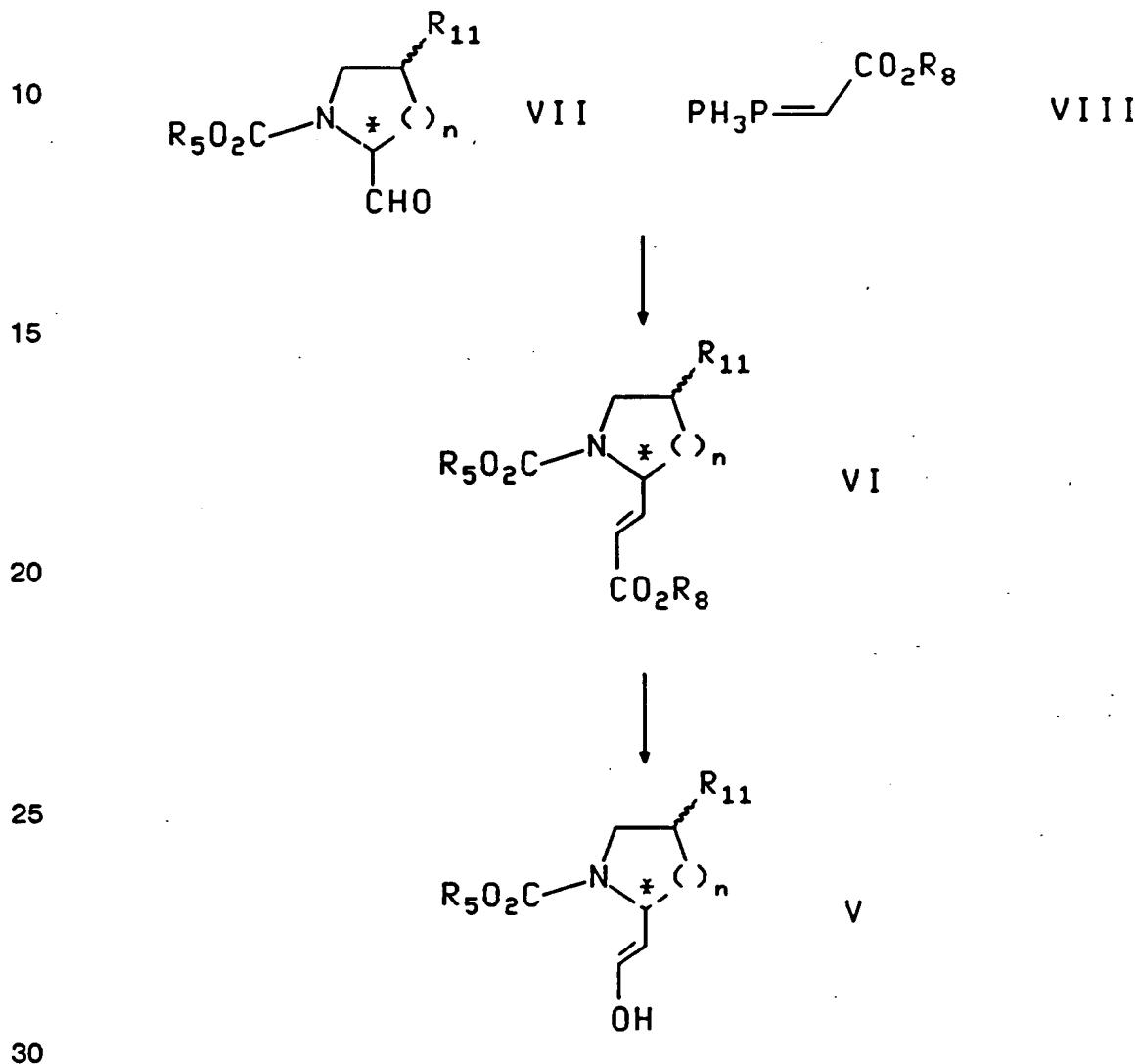
Compounds of formula IV can be prepared by reacting a compound of formula IX wherein W, m, and R₆ are as defined above with the acid chloride or symmetrical anhydride of the formula R₆OH in an inert solvent with a base. The preferred acid chloride or anhydride is trifluoroacetic anhydride. Suitable solvents include methylene chloride, chloroform as well as ethers, including tetrahydrofuran, diethyl ether and 1,4-dioxane. The preferred solvent is methylene chloride. Suitable bases include triethylamine, pyridine, and sodium hydrogen carbonate. The preferred base is

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pyridine. The reaction is conducted at a temperature of from about 0°C to about 65°C, preferably at about 25°C.

Compounds of the formula XI can be prepared using methods known to one skilled in the art, such as, for example, as outlined in International Patent Application No. PCT/GB91/00908 and European Patent Application No. 313397A.

Compounds of the formula V can be prepared using the following reaction scheme:



Compounds of the formula VI can be prepared using the Wittig reaction in an inert solvent involving compounds of the formulas VII and VIII wherein n, R₅, and R₁₁ are defined as above and R₈ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl. Suitable

solvents include ethers such as diethyl ether, tetrahydrofuran, and 1,4-dioxane. Tetrahydrofuran is the preferred solvent. The reaction is conducted at a temperature of from about -78°C to about 80°C, preferably at about 25°C.

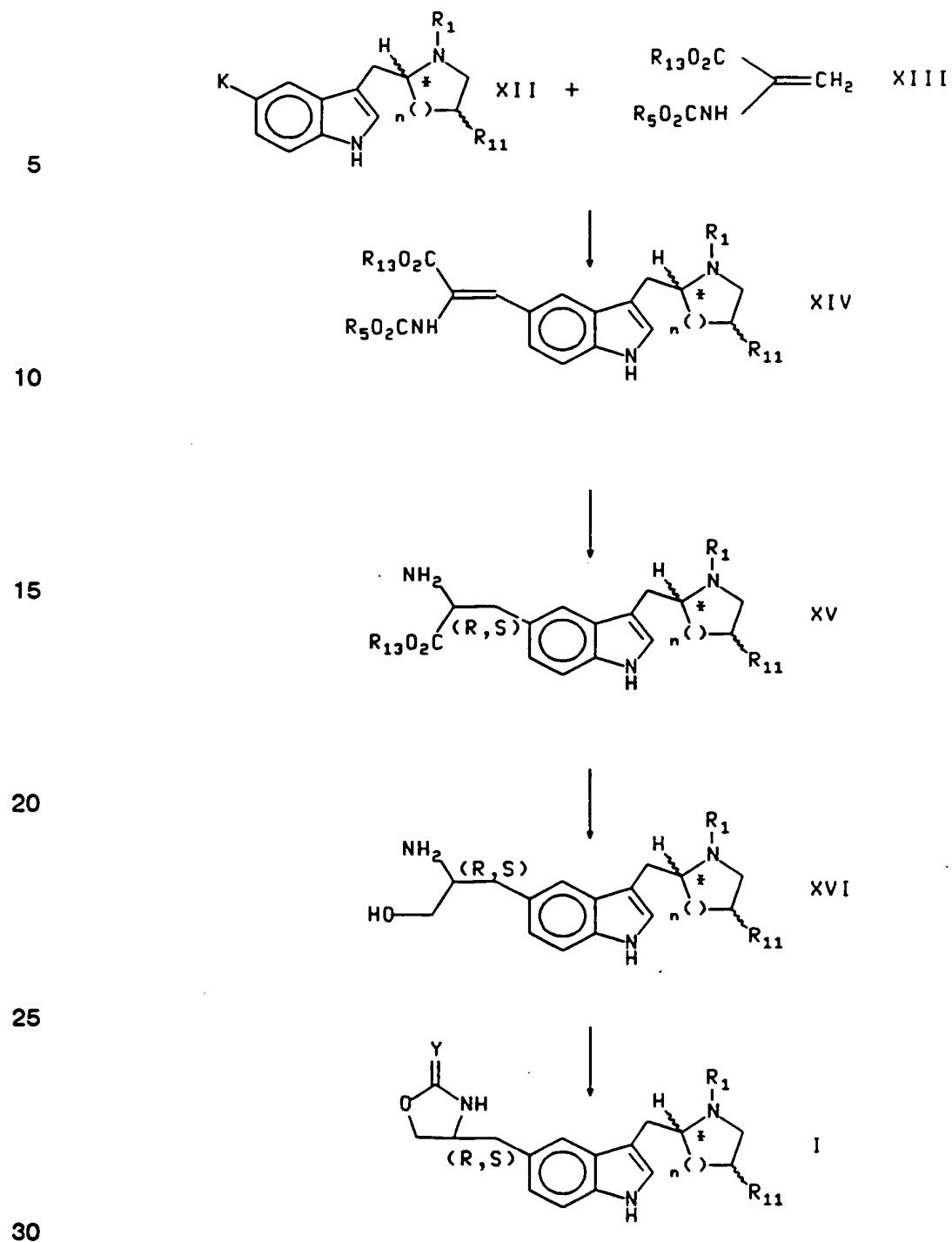
Compounds of the formula V can be prepared from a hydride reduction of a compound of formula VI wherein n, R₅, R₆, and R₁₁, are as defined above with a hydride reducing agent in an inert solvent. Suitable hydride reducing agents include lithium aluminum hydride, lithium borohydride, sodium borohydride, and diisobutylaluminum hydride. The preferred reagent is diisobutylaluminum hydride. Suitable solvents include ethers, such as diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane. The preferred solvent is tetrahydrofuran. The reduction is conducted at a temperature of from about -100°C to about 0°C, preferably from about -80°C to about -70°C.

Compounds of the formula VII can be prepared using methods known in the art, such as, for example, as outlined in S. Kiyooka, et al., J. Org. Chem., 5409 (1989) and Y. Hamada, et al., Chem. Pharm. Bull., 1921 (1982).

Compounds of the formula VIII are either commercially available or can be prepared using methods known in the art, such as, for example, as outlined in L. Fieser and M. Fieser, Reagents for Organic Synthesis, John Wiley and Sons, New York, Vol. 1, p. 112 (1967).

Compounds of formula I wherein W is (i), Z is 0, m = 1, R₃ and R₂ are each hydrogen may also be prepared via the following scheme:

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where W is (i), $Z = 0$, $m = 1$, $R_3 = H$, $R_2 = H$.

Compounds of formula XII, wherein n, R₁ and R₁₁ are as defined above and K is chloro, bromo or iodo (preferably bromo) can be prepared using methods known in the art, such as, for example, as described in WO 9206973.

Compounds of formula XIV, wherein n, R₁, R₁₁, and R₅ are as defined above and 5 R₁₃ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl, can be prepared by coupling a compound of formula XII with a dehydroalanine derivative of formula XIII wherein R₅ is as defined above (preferably benzyl) and R₁₃ is as defined above (preferably methyl), using the Heck reaction known in the art. Suitable palladium catalysts for the Heck reaction include palladium salts such as palladium (II) acetate, in the presence of a 10 phosphine such as triphenylphosphine or tri-o-tolylphosphine, preferably tri-o-tolylphosphine. Suitable bases for the Heck reaction include trialkylamines, preferably triethylamine, and suitable inert solvents include acetonitrile and N,N-dimethylformamide, preferably acetonitrile. The reaction is conducted at a temperature of from about 60°C to about 150°C, preferably at the reflux temperature of the solvent.

15 Compounds of formula XV, wherein R₁₃, R₁, R₁₁, and n are as defined above, can be prepared from compounds of formula XIV wherein R₅ is preferably benzyl, by catalytic reduction under an atmosphere of hydrogen, preferably at a pressure of from about 1 to about 3 atmospheres, or by using a hydrogen source such as ammonium formate or formic acid in an inert solvent. Suitable catalysts for either of the above 20 reactions include palladium on carbon, Raney nickel and platinum oxide, preferably palladium on carbon. Suitable solvents for either of the above reactions include C₁ to C₆ alcohols, N,N-dimethylformamide, ethyl acetate and acetonitrile. The preferred solvent is ethanol. Optionally the reaction may be conducted in the presence of an acid. Suitable acids include hydrochloric acid. Suitable solvents for use with the acid 25 include all those mentioned previously in this paragraph, preferably ethanol. All of these reactions are conducted at a temperature of from about 0°C to about 60°C, preferably at about 25°C.

Compounds of formula XVI, wherein n, R₁, R₁₁, are as defined above, can be prepared from a compound of formula XV by reduction in an inert solvent. Suitable 30 reducing agents include alkali metal borohydrides, such as sodium borohydride or lithium borohydride, or lithium aluminum hydrides such as lithium aluminum hydride. The preferred reducing agent is sodium borohydride. Suitable solvents for borohydride reducing agents include C₁ to C₆ alcohols, preferably ethanol. Suitable solvents for

aluminum hydride reductions include ethers, such as tetrahydrofuran and diethyl ether, preferably tetrahydrofuran. The reaction is conducted at a temperature of from about 25°C to about 80°C, preferably at the reflux temperature of the solvent.

Compounds of formula I, wherein W is (i), Z is 0, m = 1, R³ and R² are each H and Y is as defined above, may be prepared by condensation of compounds of formula XVI with phosgene or a phosgene-equivalent in an inert solvent in the presence of a base. Suitable phosgene-equivalents where Y is O include N,N-carbonyldimidazole, diethyl carbonate and trichloromethyl chloroformate. The preferred reagent is phosgene itself. Suitable solvents include hydrocarbons or ethers, preferably toluene. Suitable bases include inorganic bases such as sodium hydroxide, potassium hydroxide and sodium carbonate. The reaction may also be carried out with suitable thio-phosgene equivalents where Y is S, such as N,N-thiocarbonyldimidazole. The same reaction conditions used with phosgene are used with thio-phosgene, as well.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, i.e., where R, contains a carboxylate, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particular, the sodium and potassium salts. These 5 salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium, magnesium, etc. 10 These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then 15 evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction of maximum product of yields of the desired final product.

The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to as the active compounds of the invention) are 20 useful psychotherapeutics and are potent serotonin (5-HT₁) agonists and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, chronic paroxysmal hemicrania and headache associated with vascular disorders, pain, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting 25 antihypertensives and vasodilators.

The active compounds of the invention can be evaluated as anti-migraine agents by testing the extent to which they mimic sumatriptan in contracting the dog isolated saphenous vein strip [P.P.A. Humphrey et al., Br. J. Pharmacol., 94, 1128 (1988)]. This effect can be blocked by methiothepin, a known serotonin antagonist. Sumatriptan is 30 known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anesthetized dog. It has been suggested [W. Fenwick et al., Br. J. Pharmacol., 96, 83 (1989)] that this is the basis of its efficacy.

The serotonin 5-HT, agonist activity of the compounds of the present invention can be measured in in vitro receptor binding assays as described for the 5-HT_{1A} receptor using rat cortex as the receptor source and [³H]-8-OH-DPAT as the radioligand [D. Hoyer et al. Eur. J. Pharm., Vol. 118, 13 (1985)] and as described for the 5-HT_{1D} receptor using bovine caudate as the receptor source and [³H]serotonin as the radioligand [R.E. Heuring and S.J. Peroutka, J. Neuroscience, Vol. 7, 894 (1987)] 5-HT, agonist activity is defined by agents with affinities (IC₅₀'s) of 250nM or less at either binding assay.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, sublingual, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal and sublingual administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in

ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for 5 reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active 10 compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a 15 pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

20 A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., migraine) is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

25 Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μ g to 1000 μ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

30 The following Examples illustrate how the compounds of the present invention can be prepared. Commercial reagents can be utilized without further purification. Room temperature refers to 20-25°C.

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Example 1

General Procedure for the Alkylation of (R)-3-pyrrolidin-2-ylmethyl-1H-indoles

To a stirred solution of the (R)-3-(pyrrolidin-2-ylmethyl)-1H-indole (1.00 mmol) and triethylamine (0.126 g, 1.25 mmol, 1.25 eq) in either anhydrous methylene chloride, 5 anhydrous acetonitrile, absolute ethanol, or i-propanol (10 mL) at room temperature under nitrogen is added dropwise the alkylating agent (1.25 mmol). The resulting reaction solution is then stirred under nitrogen at room temperature or heated at reflux for 1 to 20 hours, depending on substrate. The resulting reaction mixture is directly column chromatographed using silica gel (approximately 25 g) and elution with 10 methylene chloride: methanol: ammonium hydroxide [9:1:0.1] to afford the title compound.

Using this procedure, the following compound was prepared:

3-[*N*-2-Methoxyethyl]pyrrolidin-2R-ylmethyl]-5-(2-oxo-1,3-oxazolidin-4S-ylmethyl)-1H-indole.

15 5-(2-Oxo-1,3-oxazolidin-4S-ylmethyl)-3-(pyrrolidin-2R-ylmethyl)-1H-indole and 2-bromoethyl methyl ether were used. Acetonitrile/ethanol (1:1) was the reaction solvent, and the reaction was heated at reflux for 3 hours. Column chromatography afforded the title compound (36%) as a light tan foam. ^{13}C NMR (CD_3OD) δ 160.9, 135.9, 127.2, 126.3, 123.8, 123.1, 118.5, 111.3, 109.2, 69.1, 68.1, 67.6, 60.9, 57.8, 54.6, 53.8, 40.4, 20 29.5, 27.2, 21.3; $[\alpha]^{25} = +12^\circ$ [c=1, MeOH]; FAB LRMS (m/z, relative intensity) 359 (23), 358 (MH^+ , 100), 188 (26); EI LRMS (m/z, relative intensity) 357 (0.1), 355 (2), 143 (25), 128 (100); HRMS calculated for $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_3$, 357.2054 found 357.2062.

Example 2

General Procedure for the Catalytic Reduction of 3-(*N*-Benzylloxycarbonyl-

25 pyrrolidin-2-ylmethyl)-1H-indoles Forming 3-(Pyrrolidin-2-ylmethyl)-1H-indoles

A mixture of the 3-(*N*-benzylloxycarbonyl)pyrrolidin-2-ylmethyl)-1H-indole (2.00 mmol) and 10% palladium on carbon (0.20 g) in absolute ethanol (15 mL) is shaken under a hydrogen atmosphere (3 atm) for 4 to 24 hours, depending on substrate. The resulting reaction mixture is filtered through diatomaceous earth, and the filtrate is 30 evaporated under reduced pressure. The residue is column chromatographed using silica gel (approximately 50 g) and elution with a solution of methylene chloride: methanol: ammonium hydroxide [8: 2: 0.2] or other appropriate solvent system to afford the corresponding 3-(pyrrolidin-2-ylmethyl)-1H-indole.

Using this procedure, the following compound was prepared:

5-(2-Oxo-1,3-oxazolidin-4S-ylmethyl)-3-(pyrrolidin-2R-ylmethyl)-1H-indole.

3-(N-Benzylloxycarbonylpyrrolidin-2R-ylmethyl)-5-(2-oxo-1,3-oxazolidin-4S-ylmethyl)-1H-indole was used. Column chromatography afforded the title compound 5 (89%) as an amorphous white solid: R_f = 0.30 in methylene chloride/methanol/ammonium hydroxide [6: 2: 0.2]; ^1H NMR (CD_3OD) δ 7.43 (br s, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.10 (s, 1H), 6.98 (dd, J = 1.4 and 8.3 Hz, 1H), 4.90 (approximately 3H, exchangeable), 4.38-4.31 (m, 1H), 4.20-4.11 (m, 2H), 3.52-3.42 (m, 1H), 3.10-2.82 (m, 6H), 2.01-1.74 (m, 3H), 1.58-1.46 (m, 1H); ^{13}C NMR (CD_3OD) δ 162.3, 10 137.3, 129.2, 127.5, 124.5, 124.0, 119.9, 112.8, 112.6, 70.7, 61.2, 47.0, 46.7, 42.2, 32.1, 31.1, 25.5; LRMS (m/z, relative intensity) 299 (3, M^+), 230 (31), 144 (18), 70 (100); HRMS calculated for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_2$ 299.1635, found 299.1628.

Example 3

General Procedure for the Formation of 3-(Pyrrolidin-2-ylmethyl)-1H-indoles Via the Palladium Catalyzed Cyclization of 1-(N-Pyrrolidin-2-yl)-3-(N-(2-halophenyl)-N-trifluoroacetylarnino)propenes

A mixture of the 1-(pyrrolidin-2-yl)-3-(N-(2-halophenyl)-N-trifluoroacetylarnino)propene (2.00 mmol), tetrabutylammonium chloride (2.00 mmol), and palladium(II) acetate (0.089 g, 0.40 mmol, 0.2 eq) in a solution of triethylamine (8 mL) and anhydrous N,N-dimethylformamide (4 mL) is heated at reflux under nitrogen for 2 hours. The resulting reaction mixture is evaporated under reduced pressure, and the residue is partitioned between ethyl acetate (25 mL) and water (25 mL). The ethyl acetate layer is removed, and the aqueous layer is extracted with ethyl acetate (25 mL). The organic extracts are combined, dried (MgSO_4), and evaporated under reduced pressure. The residue is column chromatographed using silica gel (approximately 50 g) and elution with an appropriate solvent system to afford the corresponding 3-(pyrrolidin-2-ylmethyl)-1H-indole.

Using this procedure, the following compound was prepared:

3-(N-Benzylloxycarbonylpyrrolidin-2R-ylmethyl)-5-(2-oxo-1,3-oxazolidin-4S-ylmethyl)-1H-indole.

1-(N-Benzylloxycarbonylpyrrolidin-2R-yl)-3-[N-(2-bromo-4-(2-oxo-1,3-oxazolidin-4S-ylmethyl)phenyl)-N-trifluoroacetylarnino]propene was used. Column chromatography using 1:1 ethyl acetate/hexanes afforded the title compound (40%) as a clear, colorless

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oil: R_f = 0.50 in ethyl acetate; LRMS (m/z, relative intensity) 433 (10, M^+), 298 (4), 229 (18), 204 (31), 160 (67), 143 (20), 91 (100); HRMS calculated for $C_{25}H_{27}N_3O_4$ 433.2003, found 433.2018.

Example 4

5 General Procedure for the Formation 1-(Pyrrolidin-2-yl)-3-(N-(2-halophenyl)-N-trifluoroacetylamino)propenes from the Mitsunobu Coupling of 2-Halo-N-trifluoroacetyl anilines with 1-(pyrrolidin-2-yl)-3-hydroxypropenes

To a stirred solution of triphenylphosphine (0.655 g, 2.50 mmol, 1.25 eq) and diethyl azodicarboxylate (0.39 mL, 2.48 mmol, 1.25 eq) in anhydrous tetrahydrofuran (15 mL) at 0°C under a nitrogen atmosphere is added dropwise a solution of the 2-halo-N-trifluoroacetyl aniline (2.5 mmol, 1.25 eq) in anhydrous tetrahydrofuran (5 mL). This is then followed by the dropwise addition of a solution of 1-(pyrrolidin-2-yl)-3-hydroxypropene (R, or S, or racemate, 2.00 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction solution is slowly warmed to 25°C over the course of 2 hours, and then stirred at 25°C under a nitrogen atmosphere for an additional 12 hours. The resulting reaction solution is evaporated under reduced pressure, and the residue is column chromatographed using silica gel (approximately 150 g) and elution with an appropriate solvent system to afford the corresponding 1-(pyrrolidin-2-yl)-3-(N-(2-halophenyl)-N-trifluoroacetyl-amino)propene.

20 Using this procedure, the following compound was prepared:

1-(N-Benzyl oxycarbonylpyrrolidin-2R-yl)-3-[N-(2-bromo-4-(2-oxo-1,3-oxazolidin-4S-ylmethyl)phenyl)-N-trifluoroacetylamino]propene

(R)-1-(N-Benzyl oxycarbonylpyrrolidin-2-yl)-3-hydroxypropene and 2-bromo-4-(2-oxo-1,3-oxazolidin-4S-ylmethyl)-1-trifluoroacetylaminobenzene were used. Column chromatography afforded the title compound (100%) as a clear, colorless oil; R_f = 0.45 in ethyl acetate; FAB LRMS (m/z, relative intensity) 612 (5, [MH⁺ with ⁸¹Br]), 610 (8, [MH⁺ with ⁷⁹Br]), 568 (5), 566 (8), 502 (3), 476 (4), 279 (100); HRMS calculated for $C_{27}H_{27}BrF_3N_3O_5$ 609.1087, found 609.0952.

Example 5

30 (R)-3-Hydroxy-1-(N-methylpyrrolidin-2-yl)propene

To a stirred solution of lithium aluminum hydride (0.73 g, 19.24 mmol, 2.2 equivalents) in anhydrous tetrahydrofuran (20 mL) at 0°C was added dropwise a solution of (R)-1-(N-benzyl oxycarbonylpyrrolidin-2-yl)-3-hydroxypropene (2.30 g, 8.80

mmol) in anhydrous tetrahydrofuran (20 mL). The resulting reaction mixture was heated at reflux under nitrogen for 3.5 hours. The resulting mixture was then cooled, and sodium sulfate decahydrate (10 g) was added slowly with caution. This mixture was stirred at room temperature under nitrogen for 1 hour, and then ethyl acetate (100 mL) 5 and water (1 mL) was added. The resulting mixture was stirred at room temperature under nitrogen overnight. The mixture was then filtered through Celite®, and the filtrate was evaporated under reduced pressure. Column chromatography of the residual oil using silica gel (approximately 200 g) and elution with methylene chloride/methanol/ammonium hydroxide (9: 1: 0.1) afforded the title compound (1.13 10 g, 8.00 mmol, 91%) as a clear, colorless liquid: ^{13}C NMR (CDCl_3) δ 132.6, 132.5, 69.0, 62.7, 56.6, 40.2, 31.8, 22.1; Anal. calcd for $\text{C}_8\text{H}_{15}\text{NO} \bullet 0.175 \text{H}_2\text{NO}$ [ammonium hydroxide]: C, 65.21; H, 10.88; N, 11.34. Found: C, 65.01; H, 10.71; N, 10.81.

Example 6

(R)-1-(N-Benzylloxycarbonylpyrrolidin-2-yl)-3-hydroxypropene

15 To a stirred solution of ethyl (R)-3-(N-benzylloxycarbonylpyrrolidin-2-yl)-2-propenoate (3.03 g, 10.00 mmol) in anhydrous tetrahydrofuran (75 mL) at -78°C under nitrogen was added dropwise a solution of diisobutylaluminum hydride (1.0 M in hexanes, 22.0 mL, 22.0 mmol, 2.2 eq). The resulting solution was stirred at -78°C under nitrogen for 30 minutes. The reaction solution was then allowed to warm to room 20 temperature over the course of 2 hours. A saturated solution of sodium hydrogen carbonate (50 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3 x 50 mL). The extracts were combined, dried (MgSO_4), and evaporated under reduced pressure. Column chromatography of the residue with diethyl ether/hexanes [1:1] afforded the title compound as a clear colorless oil (1.41 g, 5.40 25 mmol, 54%): ^1H NMR (CDCl_3) δ 7.40-7.25 (m, 5H), 5.75-5.53 (m, 2H), 5.20-5.00 (m, 2H), 4.38 (br m, 1H), 4.06 (br d, $J=13.7\text{Hz}$, 2H), 3.45 (br t, $J=7.0\text{Hz}$, 1H), 2.03-1.68 (m, 4H); $[\alpha]^{25} = +34^\circ$ (MeOH, $c=1.0$); HRMS calculated for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ 261.1365, found 261.1356.

Example 7

30 Ethyl (R)-3-(N-Benzylloxycarbonylpyrrolidin-2-yl)-2-propenoate

To a stirred solution of N-carbobenzylloxypyrrolidine-2-carboxaldehyde (1.17 g, 5.00 mmol) in anhydrous tetrahydrofuran at -78°C was added (carboethoxymethylene)-triphenylphosphorane (2.09 g, 6.00 mmol, 1.2 eq) as a solid portionwise. The resulting

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reaction mixture was stirred at room temperature under nitrogen for 2 hours, and then heated at reflux under nitrogen for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue was column chromatographed using silica gel (approximately 100 g) and elution with 20% diethyl ether in hexanes to afford the title compound as a clear, colorless oil (1.11 g, 3.65 mmol, 73%): ^1H NMR ($\text{CDCl}_3\text{-d}_6$) δ 7.34-7.25 (m, 5H), 6.89-6.76 (m, 1H), 5.88-5.74 (m, 1H), 5.18-5.05 (m, 2H), 4.60-4.43 (m, 1H), 4.17 (q, $J=7.1\text{ Hz}$, 2H), 3.55-3.40 (m, 2H), 2.11-2.00 (m, 1H), 1.90-1.75 (m, 3H), 1.28 (t, $J=7.1\text{ Hz}$, 3H); ^{13}C NMR (CDCl_3) [Note: due to slow nitrogen inversion two conformers of the products are seen by NMR spectroscopy] δ 166.3, 154.7, 147.9, 147.4, 136.6, 128.4, 127.9, 120.9, 66.9, 65.8, 60.4, 58.1, 57.7, 46.8, 46.4, 31.6, 30.8, 23.6, 22.8, 22.6, 15.3, 14.2.

Example 8

General Synthesis of 2-Halo-N-trifluoroacetylanilines

To a stirred mixture of the N-trifluoroacetylaniline (2.00 mmol) and sodium hydrogen carbonate (0.21 g, 2.50 mmol, 1.25 eq) in methanol (10 mL) at 0°C is added dropwise bromine (0.113 mL, 2.19 mmol, 1.1 eq). The resulting reaction mixture is then stirred at 25°C for 30 minutes. The reaction mixture is then evaporated under reduced pressure, and the residue is placed in water made acidic to pH 3 with HCl (10 mL). This aqueous mixture is extracted with ethyl acetate (3 x 15 mL). The extracts is combined, dried (MgSO_4), and evaporated under reduced pressure. The residue is column chromatographed using silica gel (approximately 50 g) and elution with an appropriate solvent system to afford the corresponding 2-bromo-N-trifluoroacetylaniline.

Using this procedure, the following compound was prepared:

2-Bromo-4-(2-oxo-1,3-oxazolidin-4S-ylmethyl)-1-trifluoroacetylamino benzene

4-(2-Oxo-1,3-oxazolidin-4S-ylmethyl)-1-trifluoroacetylamino benzene was used. Column chromatography using 7% acetone in methylene chloride afforded the title compound (45%) as a white solid: mp 157.0-160.0 °C, ^{13}C NMR (acetone- d_6) δ 159.3, 139.5, 134.6, 132.9, 130.3, 128.1, 119.9, 118.8, 115.0, 69.4, 53.7, 40.7; $[\alpha]^{25} = -28^\circ$ (MeOH, c=1); HRMS calculated for $\text{C}_{12}\text{H}_{10}\text{BrF}_3\text{N}_2\text{O}_3$ 356.9827, found 365.9824.

Example 9

General Synthesis of N-trifluoroacetylamino benzenes

To a stirred solution of the aniline (2.00 mmol) and pyridine (0.18 mL, 2.22 mmol, 1.1 eq) in anhydrous methylene chloride (10 mL) at 0°C under a nitrogen

atmosphere is added dropwise trifluoroacetic anhydride (0.31 mL, 2.19 mmol, 1.1 eq). The resultant reaction mixture is stirred at 0°C under a nitrogen atmosphere for 3 hours. Water is added (15 mL), and this aqueous mixture is extracted with ethyl acetate (3 x 15 mL). The extracts are combined, dried (mgSO_4), and evaporated under reduced pressure. If necessary, the residue is column chromatographed using silica gel (approximately 50 g) and elution with an ethyl acetate gradient in hexanes to afford the corresponding N-trifluoroacetylaminobenzene.

Using this procedure the following compound was prepared:

4-(2-Oxo-1,3-oxazolidin-4S-ylmethyl)-1-trifluoroacetylaminobenzene

10 4-(2-Oxo-1,3-oxazolidin-4S-ylmethyl)-1-aminobenzene (WO 91/18897) was used. Column chromatography using 1:1 ethyl acetate/hexanes followed by ethyl acetate afforded the title compound (70%) as a white, crystalline solid: mp 132.0-136.0°C; R_f = 0.35 in ethyl acetate; $[\alpha]^{25} = -14^\circ$ (MeOH, $c=1$); Anal. calcd for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{F}_3\text{O}_3$; C, 50.01; H, 3.85; N, 9.72. Found: C, 50.29; H, 3.81; N, 9.67.

15 Example 10

5-(2-Benzylloxycarbonylamino-2-methoxycarbonylethen-1-yl)-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole

20 5-Bromo-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole (4.65 g, 15.9 mmol), N-benzylloxycarbonyl-dehydroalanine methyl ester (5.0 g, 21.3 mmol), tri-*o*-tolyl phosphine (1.4 g, 4.6 mmol), palladium (II) acetate (350 mg, 1.6 mmol) and triethylamine (4.7 mL, 33.8 mmol) were dissolved in acetonitrile (50 mL) and heated at reflux with stirring under nitrogen overnight. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and 2M aqueous sodium carbonate. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure.

25 The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of dichloromethane: ethanol (100:0 to 80:15), to yield 1.4 g of the title compound as a foam: R_f = 0.3 dichloromethane: methanol: 0.880 aqueous ammonia (90:10:1); ^1H NMR (CDCl_3) δ 8.35 (br s, 1H), 7.80 (s, 1H), 7.56 (s, 1H), 7.50 (d, 1H), 7.40-7.28 (m, 6H), 7.04 (d, 1H), 6.40 (br s, 1H), 5.30 (s, 0.2H, CH_2Cl_2), 5.20-5.06 (m, 2H), 3.90-3.75 (br s, 3H), 3.28-3.14 (m, 2H), 2.75-2.45 (m, 5H), 2.32-2.20 (m, 1H), 1.90-1.54 (m, 4H). Anal. calcd for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_4 \cdot 0.1 \text{CH}_2\text{Cl}_2 \cdot 0.25 \text{H}_2\text{O}$: C, 68.07; H, 6.50; N, 9.12. Found: C, 67.94; H, 6.51; N, 9.29.

Example 115-(2R,S-Amino-2-methoxycarbonylethyl)-3-(N-methylpyrrolidin-2(R)-ylmethyl)-1H-indole

5-(2-Benzylloxycarbonylamino-2-methoxycarbonylethen-1-yl)-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole (150 mg, 0.34 mmol) was dissolved in ethanolic hydrogen chloride (prepared from ethanol (4 mL) and acetyl chloride (0.048 ml, 0.68 mmol)) and the resulting solution was hydrogenated over 10% palladium-on-carbon (100 mg) at room temperature at a pressure of hydrogen of 15 psi overnight. The reaction mixture was filtered through a pad of Arbacell and evaporated under reduced pressure. The residue was partitioned between ethyl acetate and 2M aqueous sodium carbonate, the aqueous phase reextracted with ethyl acetate and the combined organic phases washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel, eluting with dichloromethane : ethanol gradient (90:10 to 80:20), followed by a gradient of dichloromethane : methanol : 0.880 aqueous ammonia (80:20:0 to 80:20:1), yielding 60 mg of the title compound as a gum: R_f = 0.2 dichloromethane : methanol : 0.880 aqueous ammonia (90:10:1); $[\alpha]_D^{25} + 73^\circ$ ($c = 0.1, \text{CH}_3\text{OH}$); $^1\text{H NMR}$ (CDCl_3) δ 8.78 (br s, 1H), 7.37 (s, 1H), 7.24 (d, 1H), 7.00-6.95 (m, 2H), 5.28 (s, 0.2H, CH_2Cl_2), 3.82-3.78 (m, 1H), 3.72 (s, 3H), 3.25-3.18 (m, 3H), 3.00-2.92 (m, 1H), 2.62-2.56 (m, 1H), 2.5-2.4 (m, 4H), 2.28-2.18 (m, 1H), 1.9-1.5 (m, 6H). Anal. calc'd for $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 0.1 \text{CH}_2\text{Cl}_2$: C, 67.11; H, 7.84; N, 12.97. Found: C, 67.57; H, 7.90; N, 12.77.

Example 125-(2 R,S-Amino-3-hydroxyprop-1-yl)-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole

5-(2R,S-Amino-2-methoxycarbonylethyl)-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole (0.57 g, 1.8 mmol) was dissolved in ethanol (2.5 mL) and water (2.5 mL) and the resulting solution was added slowly to a stirred suspension of sodium borohydride (72 mg, 1.9 mmol) in water (2.5 mL) and ethanol (2.5 mL) at 0°C. The solution was heated at reflux for 3 hours and cooled to room temperature. After evaporation under reduced pressure, the resulting residue was extracted with dichloromethane (8 x 30 mL), the extract filtered to remove solid material, and the filtrate was evaporated under reduced pressure. The resulting residue was azeotroped with dichloromethane (2x) to yield 130 mg of the title compound as a white foam: R_f = 0.1 dichloromethane : ethanol : 0.880

aqueous ammonia (25:8:1); ^1H NMR (CDCl_3) δ 8.02 (br s, 1H), 7.38 (s, 1H), 7.30 (d, 1H), 7.03-7.00 (m, 2H), 5.30 (s, 0.66H, CH_2Cl_2), 3.70-3.65 (m, 1H), 3.44-3.38 (m, 1H), 3.20-3.10 (m, 3H), 2.95-2.88 (m, 1H), 2.70-2.55 (m, 2H), 2.50-2.38 (m, 4H), 2.26-2.18 (m, 1H), 1.90-1.00 (m, 7H). Anal. calcd for $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}\bullet 0.33\text{CH}_2\text{Cl}_2$: C, 65.94; H, 8.19; N, 13.31.

5 Found: C, 65.75; H, 8.28; N, 12.93.

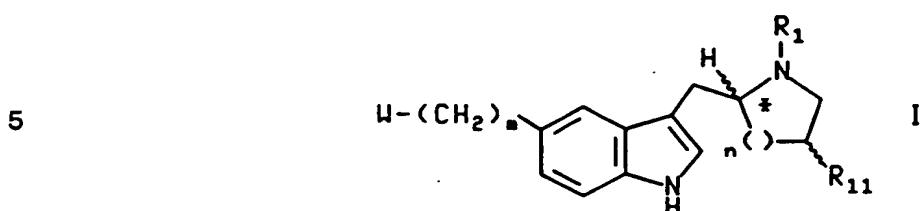
Example 13

5-(2-Oxo-1,3-oxaolidin-4R,S-ylmethyl)-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole

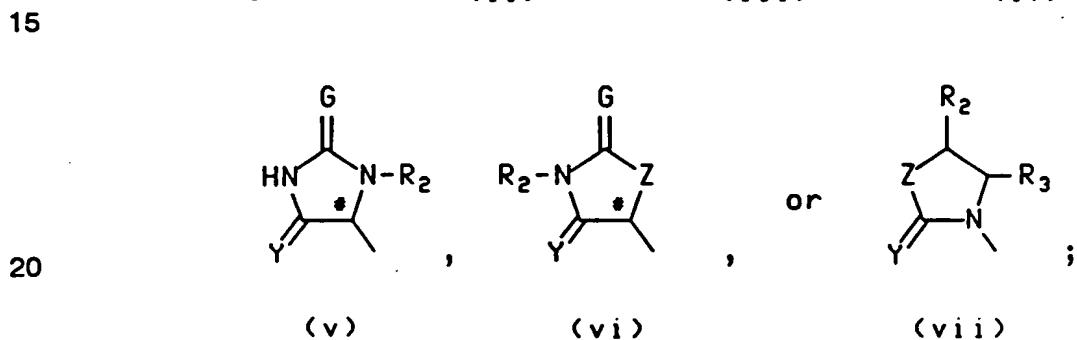
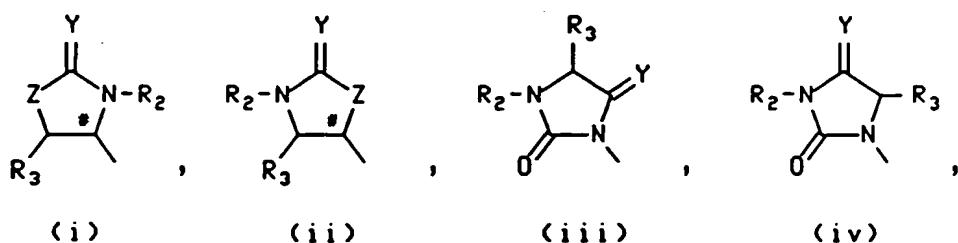
5-(2R,S-Amino-3-hydroxyprop-1-yl)-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole (50 mg, 0.17 mmol) was dissolved in toluene (2.5 mL). Potassium hydroxide (50 mg) was dissolved in water (0.8 mL) and this solution added to the above toluene solution. The resultant mixture was cooled (ice-bath) and a solution of phosgene in toluene (12.5%, 0.56 mL) was added with stirring. After cooling with an ice-bath for 15 minutes, the reaction was stirred at room temperature overnight. The organic phase was separated, the aqueous layer extracted with ethyl acetate and then dichloromethane, and all organic phases were evaporated under reduced pressure, to yield a white foam. Purification by column chromatography on silica gel, eluting with dichloromethane followed by a gradient of dichloromethane : methanol : 0.880 aqueous ammonia (90:10:1 to 70:30:2), yielded 15 mg of the title compound: R_f = 0.7 in dichloromethane : methanol : 0.880 aqueous ammonia (70:30:2); ^1H NMR (CDCl_3) δ 8.35 (br s, 1H), 7.40-7.28 (m, 2H), 7.05 (s, 1H), 6.96 (d, 1H), 5.42 (br d, 1H), 5.30 (s, 1H, CH_2Cl_2), 4.50-4.42 (m, 1H), 4.22-4.14 (m, 2H), 3.22-3.15 (m, 2H), 3.02-2.88 (m, 2H), 2.75-2.40 (m, 5H), 2.35-2.20 (m, 1H), 1.90-1.50 (m, 4H). Anal. calcd for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_2\bullet 0.5\text{CH}_2\text{Cl}_2$: C 62.43; H, 6.80; N, 11.81. Found: C, 62.66; H, 6.26; N, 11.71.

CLAIMS

1. A compound of the formula



where W is



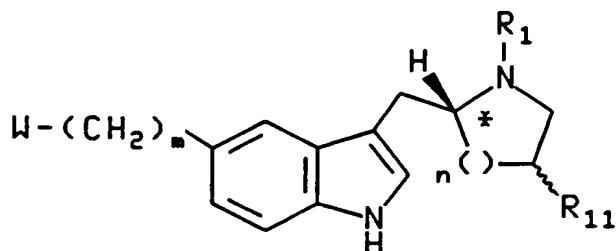
n is 0, 1, or 2; m is 0, 1, 2, or 3; Y and G are each independently oxygen or sulfur; Z is -O-, -S-, -NH, or -CH₂; R₁ is hydrogen, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl substituted with one hydroxy, C₃ to C₈ alkenyl, C₃ to C₈ alkynyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or -Q-R₄; R₂ and R₃ are each independently hydrogen, C₁ to C₆ alkyl, aryl, C₁ to C₃ alkylaryl, or C₁ to C₃ alkylheteroaryl; R₄ is cyano, trifluoromethyl, -COR₉, -CO₂R₉, -CONR₉R₁₀, -OR₉, -SO₂NR₉R₁₀, or -S(O)_qR₉; R₉ and R₁₀ are each independently hydrogen, C₁ to C₆ alkyl, C₁ to C₃ alkylaryl, aryl, or R₉ and R₁₀ may together be taken to form a three- to seven-membered alkyl ring or a three- to seven-membered heteroalkyl ring having 1 heteroatom of O; Q is C₁ to C₃ alkyl; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₈ alkyl, aryl, or C₁ to C₃ alkylaryl; q is 0, 1, or 2; a first chiral carbon is designated by an asterisk; a second chiral

carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy,

5 and the pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein the compound of formula I is

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3. The compound of claim 2, wherein the compound is the cis epimer.

4.

The compound of claim 1, wherein the compound of formula I is the S epimer having the chiral carbon designated by #.

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5. The compound of claim 1, wherein G is oxygen.

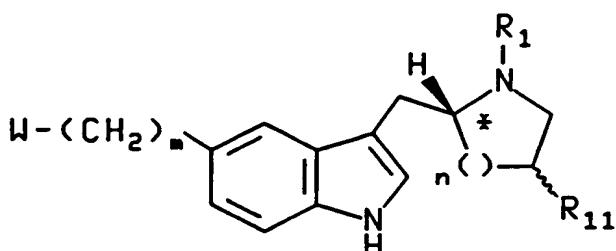
6. The compound of claim 1, wherein W is (i), (ii), (iii), or (iv); R₁ is

hydrogen, C₁ to C₆ alkyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or -Q-R₄; and

25 R₄ is cyano, trifluoromethyl, -CO₂CH₃, -CONH₂, -OH, -OCH₃, or -O-phenyl.

7. The compound of claim 6, wherein the compound of formula I is

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8. The compound of claim 7, wherein the compound is the cis epimer.

9. The compound of claim 6, wherein the compound of formula I is the S

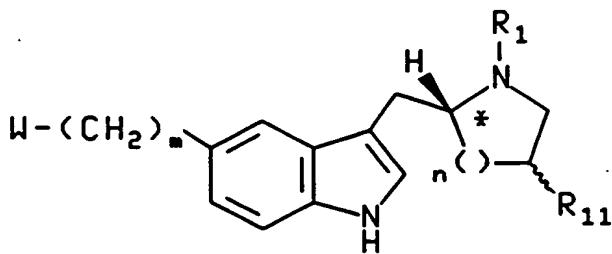
epimer having the chiral carbon designated by #.

10. The compound of claim 1, wherein W is (i), (ii), or (iii); n is 1; m is 1; R₁ is hydrogen, C₁ to C₃ alkyl, or -CH₂CH₂OCH₃; R₂ is hydrogen; and R₃ is hydrogen or -CH₂Ph.

11. The compound of claim 10, wherein the compound of formula I is

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12. The compound of claim 11, wherein the compound is the cis epimer.

13. The compound of claim 10, wherein the compound of formula I is the S epimer having the chiral carbon designated by #.

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14. The compound of claim 1, said compound being selected from 3-[(N-2-Methoxyethyl)pyrrolidin-2R-ylmethyl]-5-(2-oxo-1,3-oxazolidin-4S-ylmethyl)-1H-indole;

5-(2-Oxo-1,3-oxazolidin-4S-ylmethyl)-3-(pyrrolidin-2R-ylmethyl)-1H-indole; and 3-(N-Methylpyrrolidin-2R-ylmethyl)-5-(2-oxo-1,3-oxazolidin-4R,S-ylmethyl)-1H-

indole.

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25

15. A pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound according to claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

16. A pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission comprising an amount of a compound according to claim 1 effective in treating such a disorder and a pharmaceutically acceptable carrier.

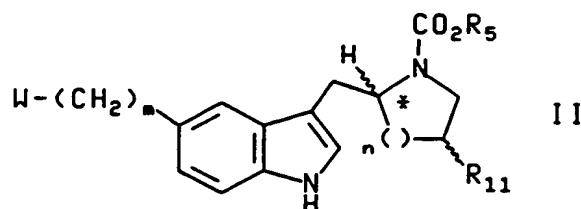
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17. A method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular

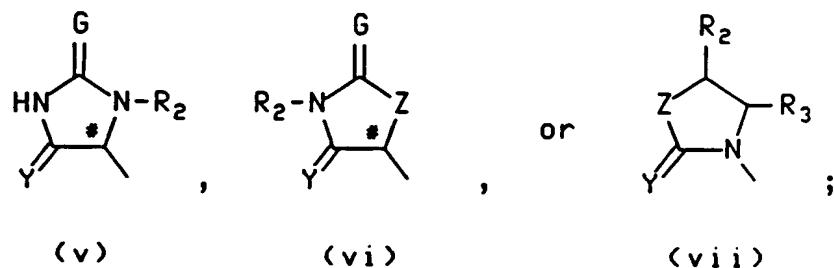
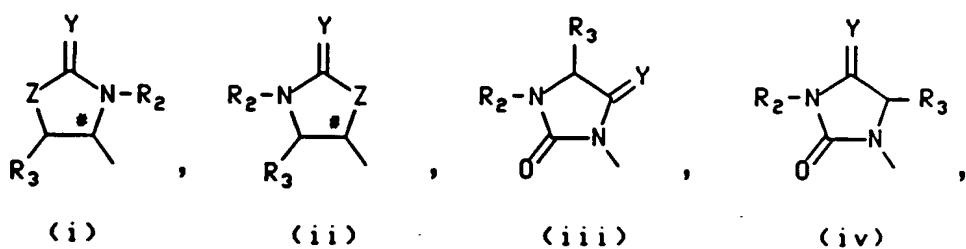
disorders comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

18. A method for treating disorders arising from deficient serotonergic neurotransmission comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

19. A compound of the formula



where W is

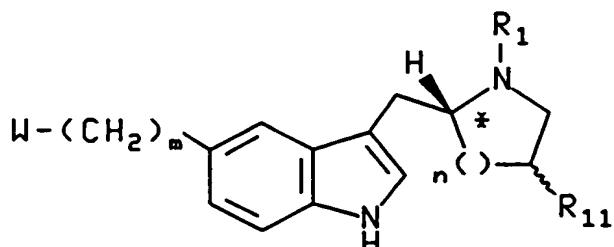


n is 0, 1, or 2; m is 0, 1, 2, or 3; Y and G are each independently oxygen or sulfur; Z is -O-, -S-, -NH, or -CH₂; R₂ and R₃ are each independently hydrogen, C₁ to C₆ alkyl, aryl, C₁ to C₃ alkylaryl, or C₁ to C₃ alkylheteroaryl; R₅ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkyl-aryl; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the

above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy.

20. The compound of claim 19, wherein the compound of formula II is

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21. The compound of claim 20, wherein the compound is the cis epimer.

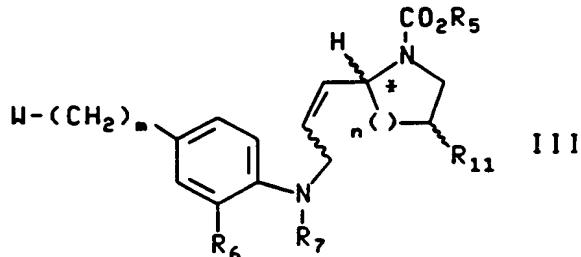
22. The compound of claim 19, wherein the compound of formula II is the ether having the chiral carbon designated by #.

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23. The compound of claim 19, wherein G is oxygen.

24. A compound of the formula

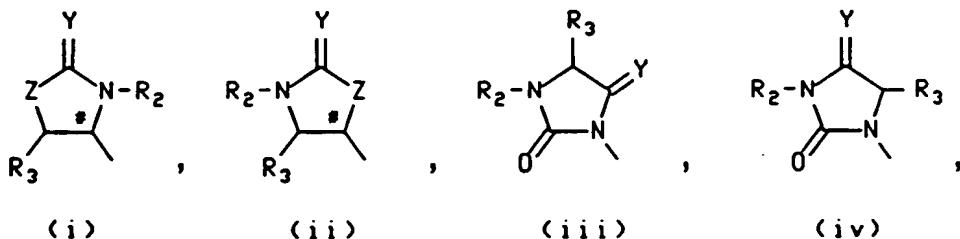
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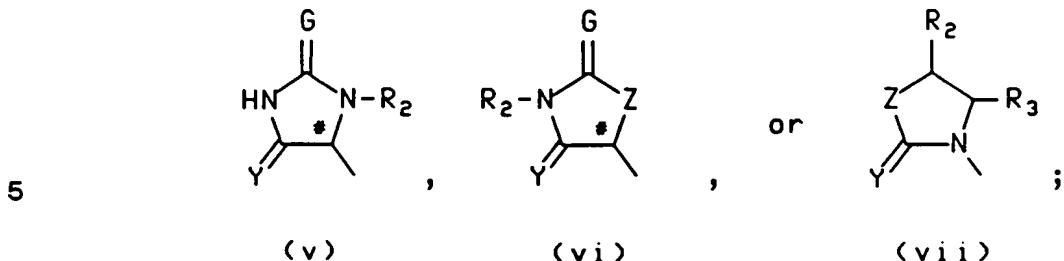


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where W is

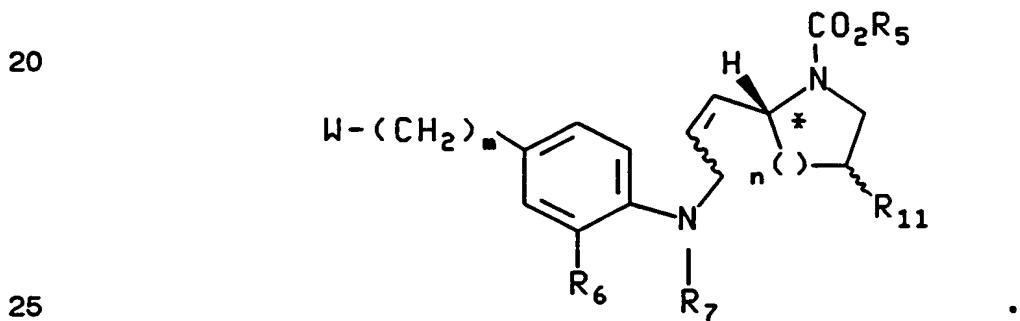
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n is 0, 1, or 2; m is 0, 1, 2, or 3; Y and G are each independently oxygen or sulfur; Z is -O-, -S-, -NH, or -CH₂; R₂ and R₃ are each independently hydrogen, C₁ to C₆ alkyl, aryl, C₁ to C₃ alkylaryl, or C₁ to C₃ alkylheteroaryl; R₅ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl; R₆ is halogen; R₇ is -COCF₃, -SO₂CH₃, -SO₂Ph, or -CO₂C(CH₃)₃; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkylaryl; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy.

25. The compound of claim 24, wherein the compound of formula III is



26. The compound of claim 25, wherein the compound is the cis epimer.

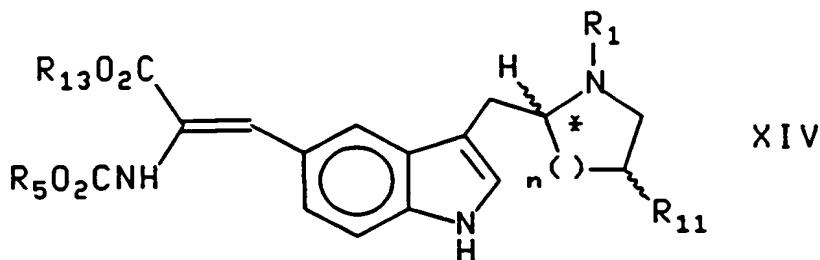
27. The compound of claim 24, wherein the compound of formula III is the S epimer having a chiral carbon designated by #.

30 28. The compound of claim 24, wherein G is oxygen.

29. A compound of the formula

-37-

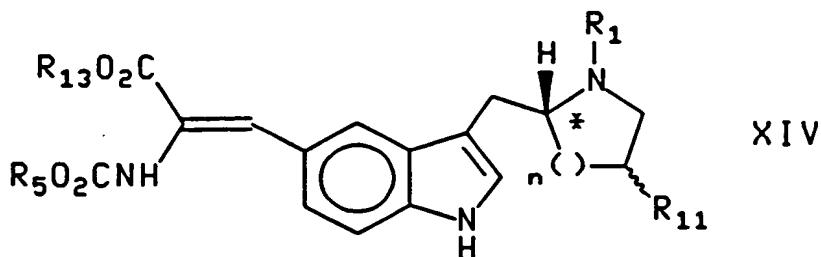
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n is 0, 1, or 2; R₁ is hydrogen, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl substituted with one hydroxy, C₃ to C₈ alkenyl, C₃ to C₈ alkynyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or -Q-R₄; R₅ is C₁ to C₈ alkyl, aryl, or C₁ to C₃ alkylaryl; R₄ is cyano, trifluoromethyl, -COR₉, -CO₂R₉, -CONR₉R₁₀, -OR₉, -SO₂NR₉R₁₀, or -S(O)_qR₉; R₉ and R₁₀ are each independently hydrogen, C₁ to C₈ alkyl, C₁ to C₃ alkylaryl, aryl, or R₉ and R₁₀ may together be taken to form a three- to seven-membered alkyl ring or a three- to seven-membered heteroalkyl ring having 1 heteroatom of O; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkyl-aryl; R₁₃ is C₁ to C₆ alkyl, aryl, or C₁ to C₃ alkyl-aryl; q is 0, 1, or 2; Q is C₁ to C₃ alkyl; a first chiral carbon is designated by an asterisk *; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy.

30. The compound of claim 29, wherein the compound of formula XIV is

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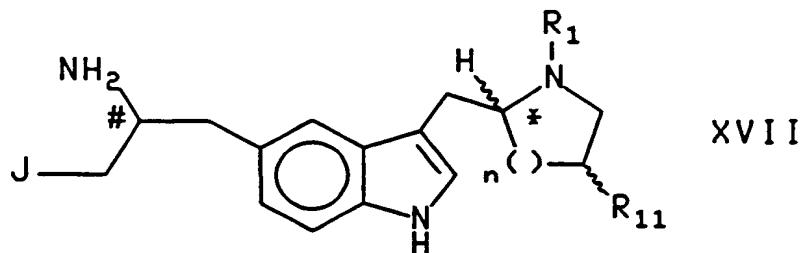


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31. The compound of claim 30, wherein the compound is the cis epimer.

32. A compound of the formula

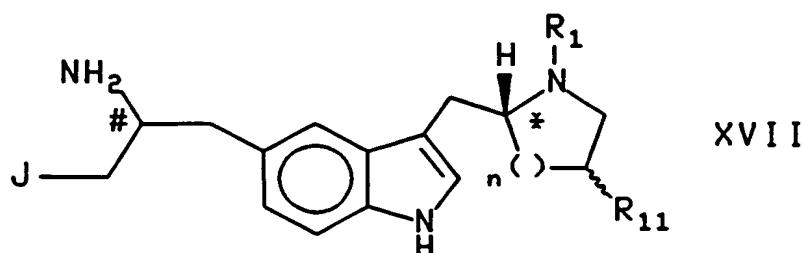
5



n is 0, 1, or 2; J is -OH or -CO₂R₁₃; R₁ is hydrogen, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl substituted with one hydroxy, C₃ to C₈ alkenyl, C₃ to C₈ alkynyl, aryl, C₁ to C₃ alkylaryl, C₁ to C₃ alkylheteroaryl, or -Q-R₄; R₄ is cyano, trifluoromethyl, -COR₉, -CO₂R₉, -CONR₉R₁₀, -OR₉, -SO₂NR₉R₁₀, or -S(O)_qR₉; R₉ and R₁₀ are each independently hydrogen, C₁ to C₈ alkyl, C₁ to C₃ alkylaryl, aryl, or R₉ and R₁₀ may together be taken to form a three- to seven-membered alkyl ring or a three- to seven-membered heteroalkyl ring having 1 heteroatom of O; R₁₁ is hydrogen, -OR₁₂, or -NHCOR₁₂; R₁₂ is hydrogen, C₁ to C₈ alkyl, aryl, or C₁ to C₃ alkyl-aryl; q is 0, 1, or 2; Q is C, to C₃ alkyl; a first chiral carbon is designated by an asterisk; a second chiral carbon is designated by #; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C₁ to C₄ alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C₁ to C₄ alkoxy.

33. The compound of claim 32, wherein the compound of formula XVII is

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34. The compound of claim 33, wherein the compound is the cis epimer.

35. The compound of claim 32, wherein the compound of formula XVII is the S epimer having a chiral carbon designated by #.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 93/01967

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 C07D413/14; A61K31/40

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1. 5	C07D

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO,A,9 118 897 (THE WELLCOME FOUNDATION LTD) 12 December 1991 cited in the application * complete document * ---	1,15
A	EP,A,0 438 230 (MERCK SHARP & DOHME LTD.) 24 July 1991 cited in the application see claims ---	1,15
A	EP,A,0 313 397 (THE WELLCOME FOUNDATION LTD) 26 April 1989 cited in the application see claims ---	1,15

¹⁰ Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- "Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

Date of Mailing of this International Search Report

03 JUNE 1993

21. 06. 93

International Searching Authority

Signature of Authorized Officer

EUROPEAN PATENT OFFICE

VAN BIJLEN H.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category ^a	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,A	WO,A,9 206 973 (PFIZER INC.) 30 April 1992 * complete document * ---	1,15
P,A	WO,A,9 213 856 (PFIZER INC.) 20 August 1992 see claims -----	1,15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/01967

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 17 and 18 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 9301967
SA 71337

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 03/06/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9118897	12-12-91	AU-A-	7957091	31-12-91
		EP-A-	0486666	27-05-92
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		CN-A-	1053429	31-07-91
EP-A-0313397	26-04-89	AU-A-	2418188	27-04-89
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		CN-A-	1062529	08-07-92
WO-A-9213856	20-08-92	AU-A-	1263792	07-09-92